Lightning Talk Slides

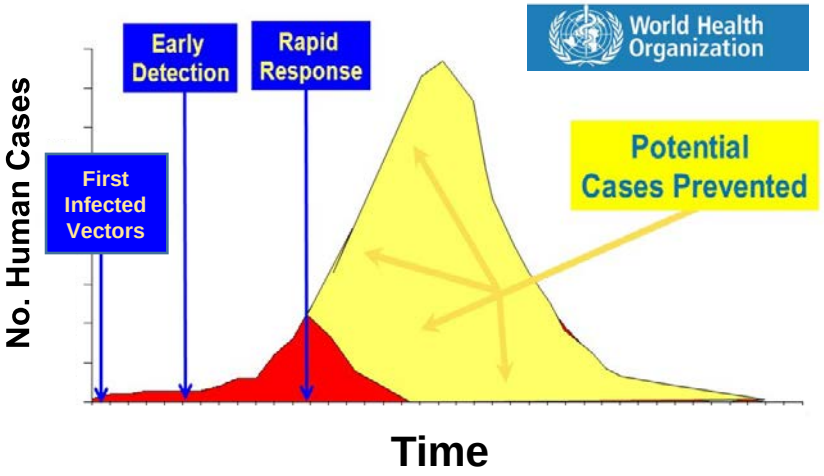
Real-time Pathogen Surveillance

PIs: Megan Fritz, David Serre, David Hawthorne
Institutions: UMCP, UMB

Competition Sensitive

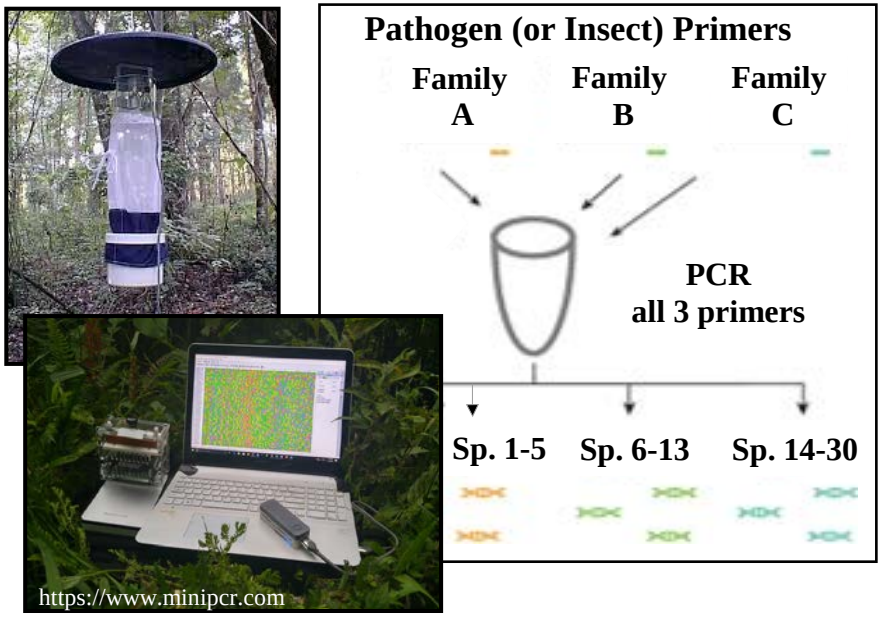
Impact

Early pathogen detection is key to epidemic prevention.



Current surveillance approaches do not allow for rapid pathogen detection, and cannot detect novel or emerging pathogens.

Project Overview & Goal



Leverage existing trapping and portable genomic technologies to develop a field-deployable vector-borne pathogen surveillance system that enhances the speed and scope of pathogen detection.

Teaming Objectives

Current capabilities:
Vector sampling and ID, genomics and bioinformatics

Potential teaming interests:
Trap optimization (engineer), Software development

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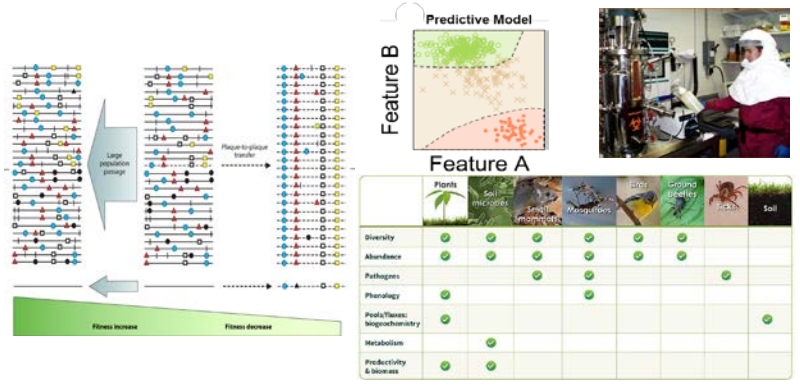
Hawthorne: djh@umd.edu

Michael Dickens, PhD, Battelle

Project Overview

- Battelle plans to leverage our experience with deep metagenomic sequencing of environmental samples and *in vitro / in vivo* laboratory cultivated agents, coupled with cutting edge bioinformatics, proprietary algorithms, and unique databases of pathogen and host factors to identify low frequency mutational patterns in viral quasispecies.
- Using time-phased repeated analysis of experimental testbeds, Battelle will employ statistical modeling, in conjunction with machine learning, to identify and predict the risk of increased virulence and potential for cross-species movements.



Teaming Overview and Objectives

- **Current team:** Battelle + experienced teammate(s) in environmental host reservoir-pathogen interactions and pandemic modeling
- **Relevant capabilities and strengths:**
  - Microbial collection, detection, identification, and characterization, including the National Ecological Observatory Network (NEON) Program
  - State-of-the-art BSL-2/ABSL-2 and BSL-3+/ABSL-3 testbeds
  - Advanced metagenomics, bioinformatics, risk prediction modeling and machine learning methods development and applications
  - Proprietary, comprehensively curated databases of pathogen threat sequences and host associations
- **Technical Challenges:** Selection of appropriate virus model(s), testbeds, and development of tools to accurately identify and predict species jump.

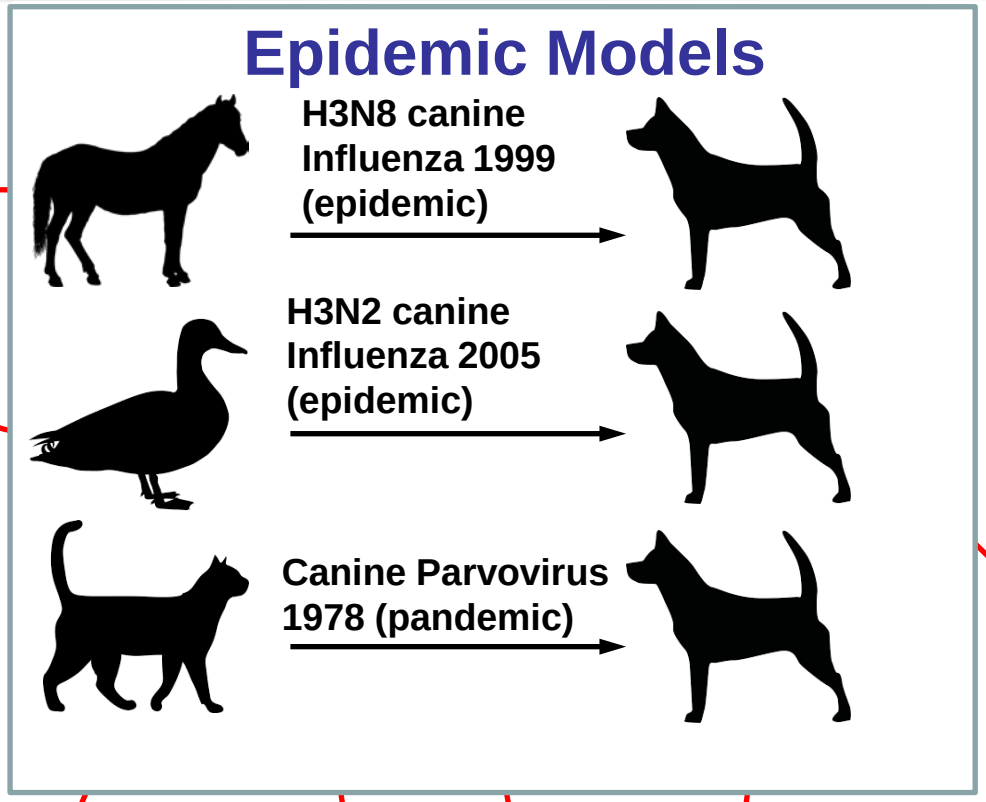
Impact

- This program will result in cutting-edge experimental testbeds and bioinformatic tools for identifying low frequency mutations responsible for viral swarm phenotypic changes and unique predictive modeling tools that identify potential pandemics, and interventions, prior to their occurrence.
- **Potential adjacent application:** Therapeutic efficacy predictive modeling
- **Metrics and Milestones:**
  - **Year 1**: Select appropriate virus model(s), establish experimental testbed(s), and apply bioinformatic pipelines to identify low frequency mutations associated with viral swarm changes
  - **Year 2**: Refine bioinformatic pipelines, apply predictive modeling tools, and verify data supports cross-species movements
- **Technology transfer:** Team Battelle will seek to transfer the technology to domestic military and public health entities for worldwide deployment.

Michael Dickens, PhD – dickensm@battelle.org – 614-424-4842

BATTELLE

Colin Parrish – Cornell University
Viral and Host Factors allowing Epidemic Emergence?



Geoghegan Open Biol.7: 170189.

The Mérieux Foundation USA

The ***Fondation Mérieux*** is a non-profit organization that conducts infectious disease research in LMICs.

As part of a consortium to address technical objectives of PREEMPT, we can provide:

- Logistics, infrastructures, and personnel in geographic hotspots for collection of human and animal samples,
- Multiplex molecular testing multiplexed capacities in BSL-2+ and BSL-3,
- Culture of viruses and deep-sequencing,
- Quality-assured repositories of samples and isolates,
- On-site experimental validation of model predictions,
- On-site experimental validation and safety/efficacy of methods to preempt viral jump across species.

- Headquartered in France, China and the USA. Bureaus in Senegal, Madagascar, Lebanon and Laos,
- Laboratories in France (INSERM Institute for Infectious Diseases including BSL-4) and China (Chinese Academy of Medical Sciences),
- International research network: GABRIEL (16 countries/20 labs including LMICs institutions),
- Supports 8 national research labs (Mali, Madagascar, Laos, Cambodia, Bangladesh, Lebanon, Brazil and Haiti), with molecular biology labs, BSL-2+ and BSL-3,
- Member of the Global Virus Network (41 Centers of Excellence in Virology worldwide),
- Past history of collaboration with European and US research institutions (NAMRU-2, DTRA, CDC).

We are interested in partnering with a scientific team to which we bring our strong footprint for infectious disease research in countries with high risk of zoonosis emergence

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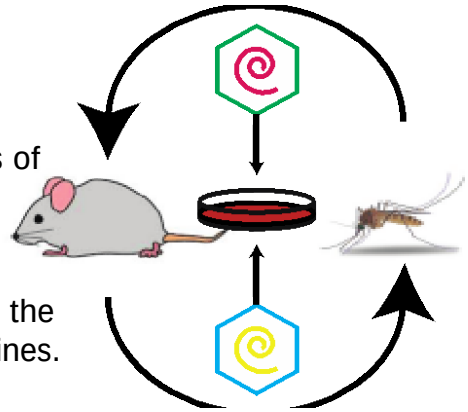
Kenneth Stapleford, NYU School of Medicine

Project Overview

Objective 1: Identify and characterize arbovirus evolutionary and epidemic trajectories.

Objective 2: Understand the driving forces of arbovirus evolution, transmission, and pathogenesis.

Objective 3: Exploit these mechanisms for the development of antiviral therapies and vaccines.



Approach 1: *In vitro* systems to study arbovirus transmission and evolution. (Host and viral factors)

Approach 2: Powerful *in vivo* animal models to study/manipulate viral evolution in real-time (Transgenic animals, Co-infections).

Approach 3: Transmission system to study the dynamics of arbovirus infections. (From the first cell infected to the last)

Teaming Overview and Objectives

Our Team (Elfie De Jesus (Technician), Gaby Noval (Postdoc), Margarita Rangel (Graduate student))

- Identified the epidemic strain of CHIKV in the lab in just 7 days.

- Identified multiple, novel evolutionary events in CHIKV that have significant epidemic potential.

NYU SOM: BSL2, BSL3 (insectary and animal facility), select agent facility, Genomics, Proteomics, Metabolomics, High-throughput screening, Single-Cell systems, microscopy, and bioinformatics core facilities and experts.

Impact

- Identify evolutionary trajectories of arbovirus through time and space (What is possible?)
- Define the temporal and spatial dynamics of arbovirus infections (viral and host responses)
- Reveal essential viral and host pathways and components required or arbovirus evolution, transmission, and pathogenesis.
- Together, these will provide novel targets for vaccine development and anti-viral/anti-pathogen evolution therapies.

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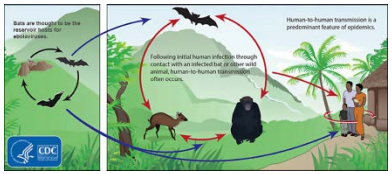
Functional Genomics Studies of Bat Transmission

Gustavo Palacios/Jonathan Towner/Stuart Nichol/Mariano Sanchez-Lockhart USAMRIID/CDC/UNMC

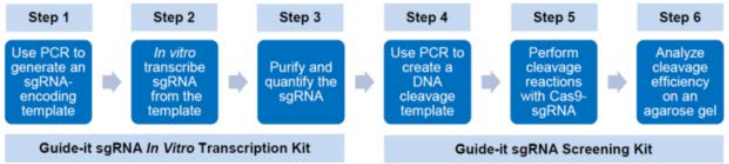
Project Overview

- **Main Goal**: Identify mechanisms to decrease virus shedding from Bats to reduce animal-to-human virus **jump opportunities**
  - Utilize targeted approaches of **comparative genomics** to identify common traits in fruit- and insectivorous bats
  - Identify "animal-to-human" genetic bottlenecks that model viral **transmission** between Bats and Primates
  - Utilize **genomics engineering and environmental** tools to limit virus transmission from Bats

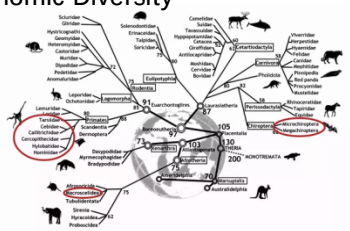
Transmission



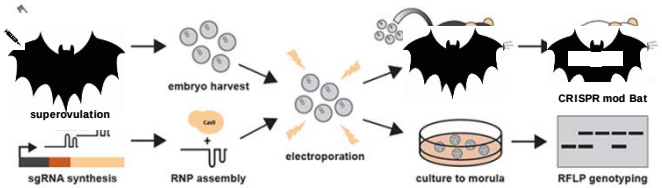
High-Throughput Genomic Screenings



Genomic Diversity



Genomic Engineering



Teaming Overview and Objectives

- USAMRIID Center for Genome Center:
  - Deployable Near-Real Time Metagenomics, Pathogen Discovery and Advanced Pathogen Characterization Capabilities: *NEJM* (PMID 26465384), *Science Adv* (27386513), *CHM* (27569558), *Nature* (28405027 and 28538723).
  - Viral Population Genomics: Cell Reports (PMID: 26365189), Nature (26934220)
  - Functional Genomics, NHP testing capabilities to model Bat-NHP transmission.
- CDC Viral Special Pathogen Branch:
  - Unique transmission modeling capabilities including the only Bat colony of Rousettus aegyptiacus to perform Bat transmission experiments for filovirus. *Sci Rep* (28821722), *Nature Com.* (28194016), *EID* (25272104), *J Wildl. Dis* (25919464 and 25375951), *Viruses* (26120867).
- University of Nebraska Medical Center:
  - Genomic engineering (CRISPR/Cas9 and Gene Drives) and Immunomics

CDC and UUSAMRIID had received DOD funding for the last 4 years to support and enhance these capabilities (DOD #**HDTRA1-14-1-0016**). Bat Genome, Transcriptome and Reagents had been generated under this study (*BMC Genomics*, PMID: 26643810).

The project will be facilitated by CDC and USAMRIID deployed capabilities in the relevant geographical area (Western Africa).

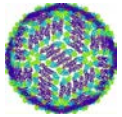
Technical Assistance needed: Expansion of the model beyond the *Filoviridae* family and to other geographical areas.

Impact

- Comprehensive understanding of the host and viral factors determining the success of filovirus transmission between bats and primates.
- Identification of common traits involved in virus shedding among different species of bats.
- Proof-of-principle of the feasibility of limiting transmission ("shedding") using genetic engineering and/or environmental triggers.

Gustavo Palacios – gustavo.f.palacios.ctr@mail.mil – 240.446.2513

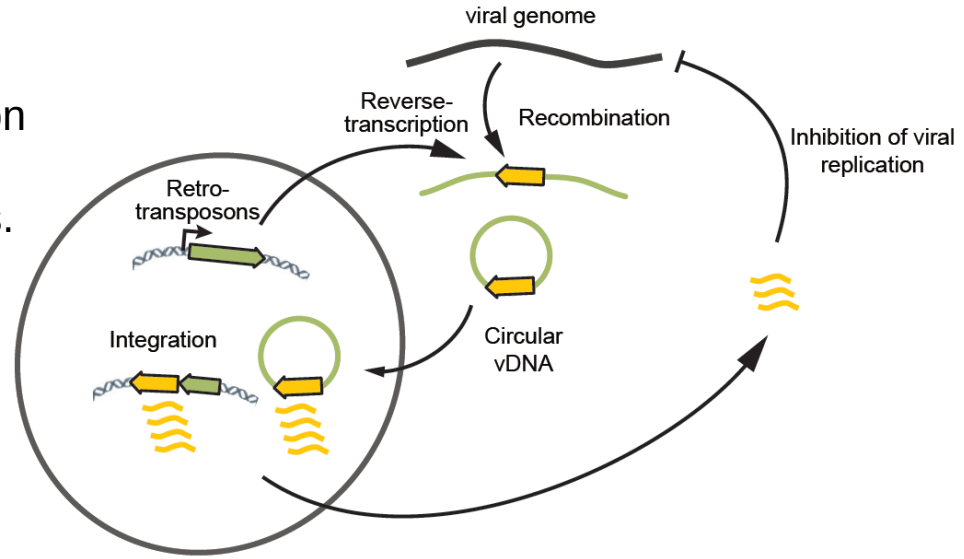
Arboviruses



Vectors

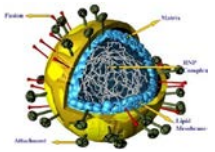
Task 1: Identification and classification of viral elements enabling zoonotic transmission. Adaptation experiments. (Machine learning/AI IBM, UCSF)

Immunological memory

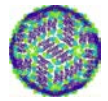


Task 2: Insects as environmental probes: identification of viral sequences in mosquitoes populations. Mathematical models predicting the risk zoonotic transmission. (Sequencing, ML/AI, models, UCSF/IBM

Broad spectrum antivirals

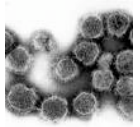


RSV



Flavis

VSV



La Cross

Task 3: Optimization of a novel class of antivirals (Proteostasis) (Screenings, medicinal chemistry, animal models, Stanford, Open Philanthropy)

Vasilakis, UTMB

DISARM: Disrupting Infection by Sylvatic Arboviruses via Research and Management

Project Overview

- **Overall Goal:** discover mechanisms that allow zoonotic, sylvatic arthropod-borne viruses (arboviruses) to jump species boundaries and cause human disease and utilize this information to anticipate and avert arbovirus emergence
- **Research Approach:** leverage our 2 active field study sites in Sarawak, Malaysian Borneo and Manaus, Brazil to prospectively investigate the ecology of sylvatic arbovirus circulation and spillover; capitalize on the viruses and vectors collected to investigate genetic signals of virus emergence potential; utilize these ecological and evolutionary data to develop and refine model-based predictions of emergence; implement control measures guided by model outputs
- **Specific Plan:** Phase I: 1. Characterize host and vector diversity and ecology, virus diversity and contact between humans and sylvatic arbovirus cycles in the field; 2. Transfer key vectors and viruses into the lab for vector competence studies, adaptation *in vivo/in vitro*, genome analyses; 3. Utilize data from 1 and 2 as foundation for models extending from virus structure to systems ecology. Phase II: Enact rationally-designed control measures, such as genetically modified vectors and/or microbiome modifications, novel vaccine approaches and therapeutic/preventative therapy based on antibodies. In Phase II, we will also integrate our developed models of risk assessment and validate emergence outcomes based on our developed intervention approaches.

Teaming Overview and Objectives

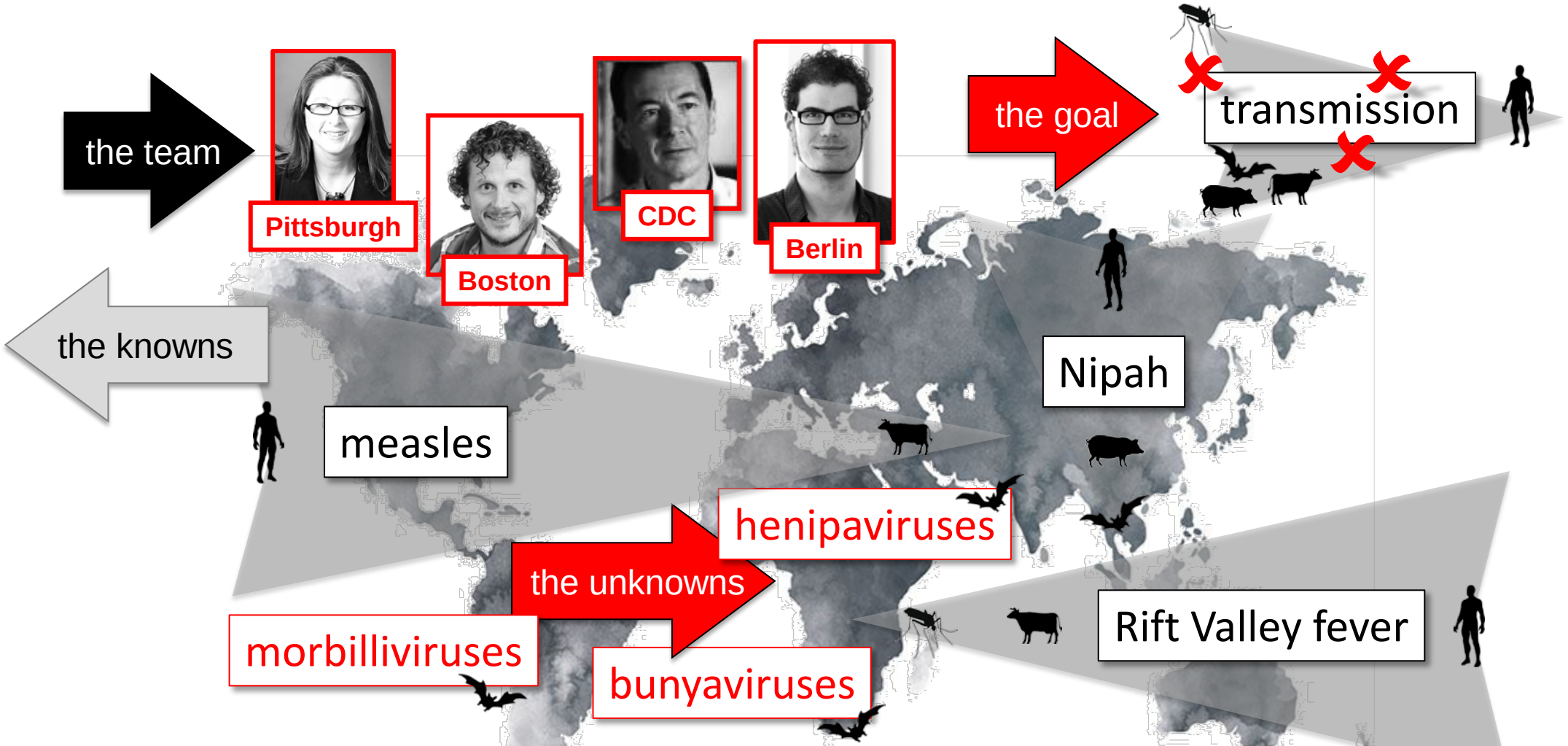
- Multidisciplinary team anchored by UTMB with partners from NMSU, JHU, CIES, WUSL, UPR, UNIMAS (Malaysia), UFAM (Brazil) and QU (Australia) possesses most key skills and resources needed to accomplish goals.
- Team members are world leaders in their disciplines and have been in the vanguard of the study of arbovirus emergence and control & host/vector predictive analytics
- Many team members have long history of collaboration
- UTMB is the only academic institution with functional Biosafety facilities to BSL4 including insectaries, WRCEVA, long term collaborative agreements with Malaysian and Brazilian partners, as well as DoD and HHS collaborations.
- Our team will require expertise in structural modeling

Impact

- We will integrate cutting edge technologies in surveillance (ie UAVs), genetic analysis, and predictive modeling to pinpoint sources (geographical, organismal and genetic) of arbovirus emergence; tools may be extended to other pathogens
- Key milestones: comprehensive characterization of arbovirus-vector-host networks, particularly in the canopy, determination of adaptive potential of existing and novel arboviruses, integration of such data into model-based predictions of emergence, and implementation of control measures focused on specific routes of emergence.
- Our team will pursue technology transition by establishing relationships with commercial partners for scale up and commercialization

Prof. Nikos Vasilakis, PhD, FASTMH; Dept. of Pathology and Center for Biodefense and Emerging Infectious Diseases, University of Texas Medical Branch, Galveston, TX 77555-0609 – nivasila@utmb.edu – 409.772.3938

PRESCIENCE: …to know … before …



the goal of this project is to engineer pre-zoonotic pathogens, model their in vitro and in vivo trajectories and intervene in animal reservoirs to subvert cross species transmissions

Marco Vignuzzi, Carla Saleh, Institut Pasteur

Project Overview

- Worldwide sampling of sylvatic and urban mosquitoes, experimental evolution of arboviruses in reservoir hosts and mosquitoes, intervention strategies in the mosquito vector (lab and field)
- Sampling of field sites to identify arboviruses, evolve viruses in vitro and in vivo, identify factors driving evolution, target factors by molecular approaches
- Phase I: mosquito collection (field), experimental evolution (lab), mathematical modeling of infection and transmission (lab), intervention strategies in vitro and in vivo (lab)
- Phase II: vector intervention strategies based in testbed or semi-field conditions, scale-up modeling for field intervention

Teaming Overview and Objectives

- **Institut Pasteur Paris**: Vignuzzi lab (experimental evolution), Saleh lab (mosquito-virus interactions), Lambrechts lab (mosquito genetics/transgenics), Failloux lab (entomology, vector competence), Simon-Lorière (field sampling), Cauchemez lab (ecological/epidemio modeling)
- **Institut Pasteurs worldwide** (sampling and testing): Polynesia, New Caledonia, Cambodia, Madagascar, Gabon, CAR, French Guiana, Brazil, Uruguay)
- **Other partners**: Stapleford (NYU), Weger (VirginiaTech), LathamBiopharmGroup (USA)
- **Institutional assets** (BSL3 facilities in all institutes, sequencing facilities, >100 years of cooperation with local governments)

Impact

- New ecological and entomological data on world scale, identify key adaptations allowing species jumps, identify targets in arbovirus transmission cycle, localized intervention strategies at vector interface
- New applications for vector control, vector transgenics, vaccines, antivirals
- Technology transition requires partnering for large-scale mosquito breeding

Contact Information – marco.vignuzzi@pasteur.fr

Multi-Scaled Models to Predict And Mitigate Arbovirus Spillover (M-PAMS)

MO Ruiz, PhD
RL Smith, DVM, PhD

University of Illinois at Urbana-Champaign

TARGET. Highly refined, spatiotemporal models with dynamic inputs to identify locally relevant biological hotspots. *Where & when is spillover most likely?*

PREDICT. Field-based observations, satellite imagery, machine learning and genomics of pathogen, vectors, and hosts to predict the risk of emergence events.

MITIGATE. Employ signatures of transmission bottlenecks and experimental targeting strategies to reduce risk.

Novel predictive models of tick-borne encephalitis

Woese Institute for Genomic Biology: Infection Genomics for One Health & NCSA

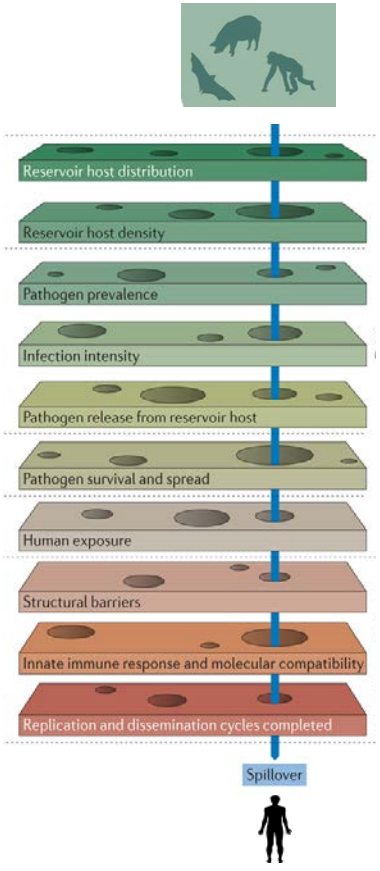
Next generation genomics and analytics

CDC Midwestern Center of Excellence in Vector-Borne Diseases. *Deep sequencing, Vector biology, Eco-epidemiology*

IMPACT. Effective mitigation of risk to DoD personnel and their working field environment through delivery of:

- Real-time predictive **models**
- In-time **field detection systems**
- New generation physical warrior barriers (**anti-vector cloth-based uniforms**)
- Scientific underpinning for next- generation, fast acting **vaccines** for warriors and animals

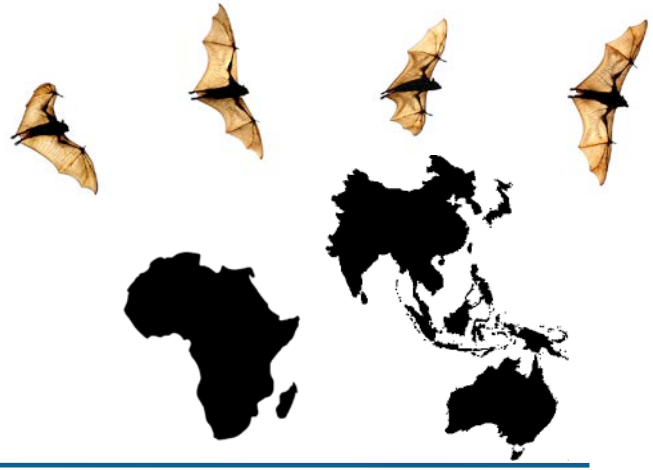
Raina Plowright, Montana State University – Bat virus phylodynamics



Plowright et al. *Nature Reviews Microbiology* 2017

Project Overview

- Our aim:
  - Measure viral genetic diversity in the reservoir
  - Identify bottlenecks in the zoonotic transmission chain
  - Model the evolutionary epidemiology of bat-borne viruses
  - Test hypotheses from field & modeling in the lab (BSL3/BSL4)
- Why PREEMPT: develop a scalable framework for virus evolution at the source of zoonotic spillover
- Key steps:
  - Field virus isolation and deep sequencing
  - Experimental approaches
  - Phylodynamic framework



Teaming Overview and Objectives

- R. Plowright (MSU), J. Lloyd-Smith (UCLA), V. Munster (NIH/RML), N. Bharti, P. Hudson (PSU), A. Peel, H. McCallum (Griffith), O. Restif (Cambridge)
- Experience:
  - field-based wildlife epidemiology on multiple continents,
  - Viral discovery
  - State-of-the-art mathematical and statistical modeling
  - BSL3/BSL4 experimental infections
- World-leading publications setting the trend in interdisciplinary research on wildlife and zoonotic diseases
- Active research programs on major zoonotic viruses (Hendra, Ebola, Nipah, MERS-CoV, SARS-CoV, Lassa virus), bat ecology and spillover
- Technical challenges:
  - obtaining viral sequences with spatiotemporal resolution to infer selective pressures at multiple scales
  - Development of interventions

Impact

- Develop reliable evolutionary inference from incomplete observations, by combining multiple sources of data
- Multiscale viral evolutionary framework from host cells up to ecosystem
- Host reservoir and spillover prediction using quantifiable data
- Potential applications:
  - novel approach to analyze deep sequencing data in ecological context
  - Predict impact of interventions on virus evolution
  - Immunopharmacology

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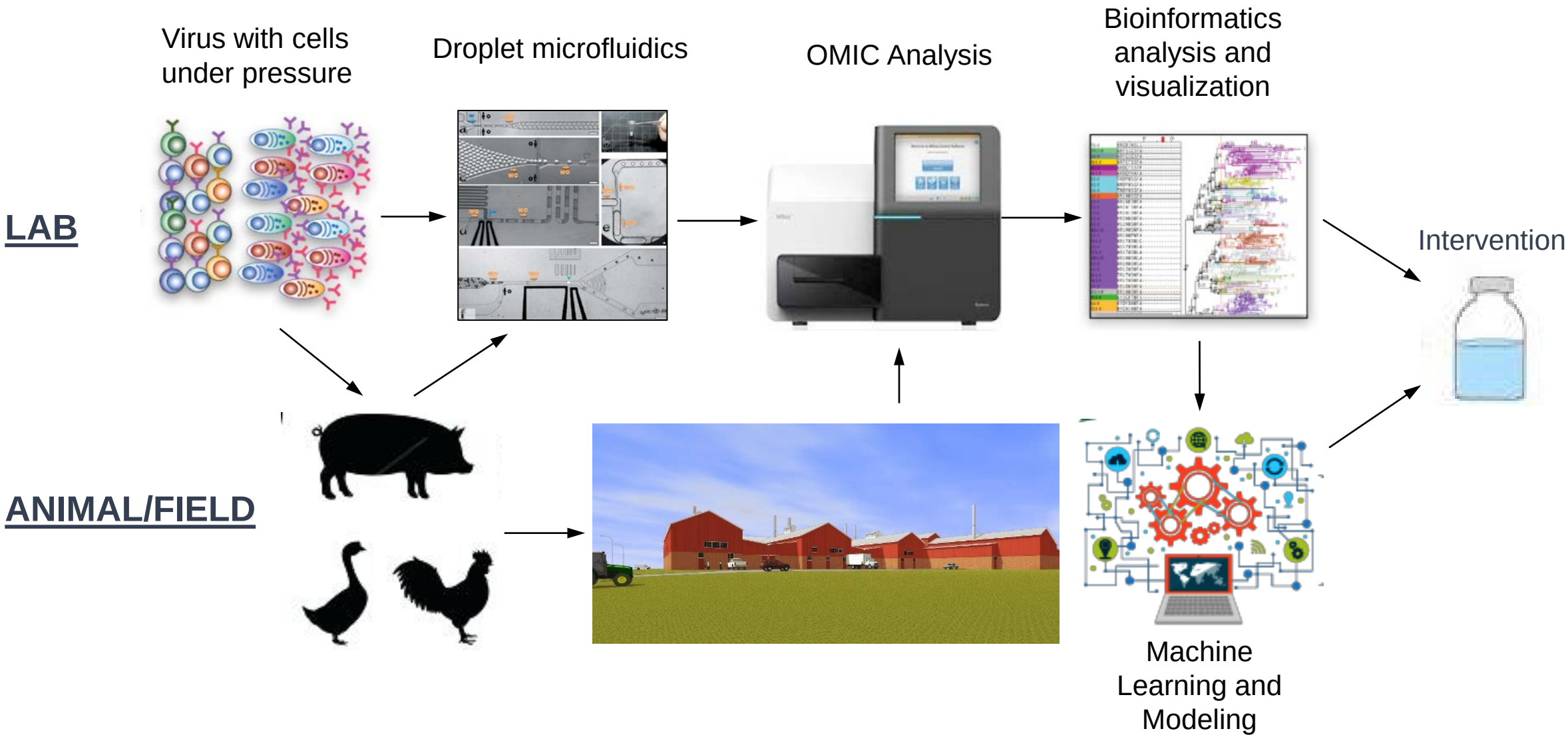
PREEMPT: Preventing Emerging Pathogenic Threats

Jared D. Evans, PhD. Johns Hopkins Applied Physics Laboratory. jared.evans@jhuapl.edu



Artificial Ecosystems: Wet Markets, Barnyards, and Terraforma

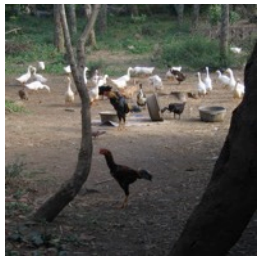
Colorado State University

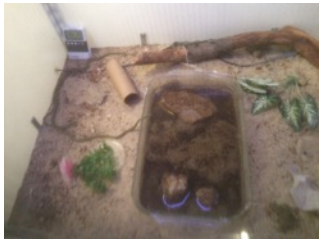
Artificial Barnyards and Wet Markets

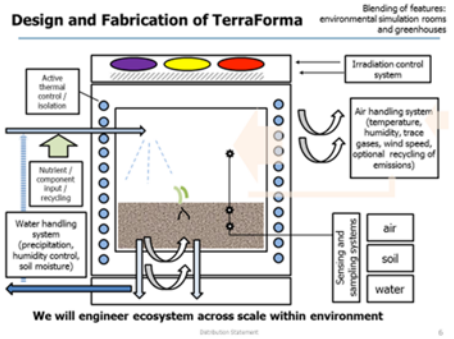
- Mixed species (e.g. ducks, chickens, pigeons, quail, rats, pigs)
- Caged vs. free vs. mixed
- ABSL3 containment
- Test pathogen transmission from animal to animal under realistic conditions
- Rapid turnaround for experiments

Indonesia

CSU BSL3







Terraforma Ecosystems

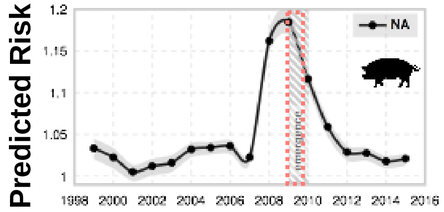
- Simple (e.g. vector-based transmission) vs. complex (e.g. weather and sensors)
- Goal: realistic simulation of natural world transmission events in variable environments

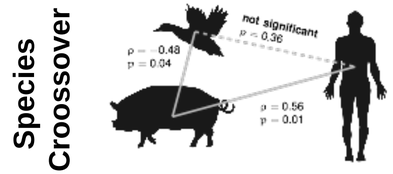
Richard.Bowen@colostate.edu

PI: Ariel Weinberger, Autonomous Therapeutics
Team: University of Chicago, Gladstone Institutes/UCSF & Col. State University

Sampling & Genomics in animal reservoirs
(CSU, UChicago & Autonomous)

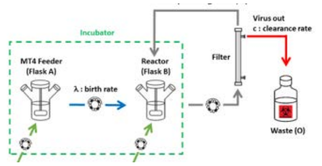
Machine Learning to predict risk
(UChicago & Autonomous)



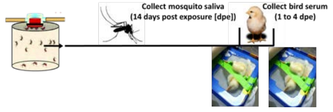


In vitro & in vivo systems to test models, viruses & therapies
(Autonomous & CSU)

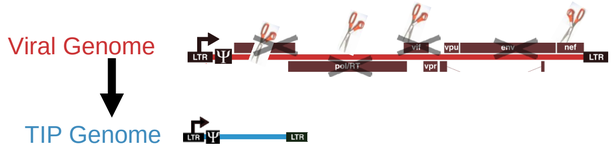
Bioreactors to reproducibly track viral evolution (e.g., GoF)

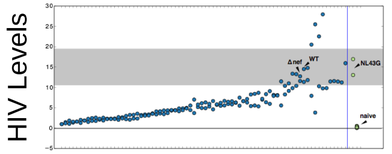


Multi-species communities (here: vector-bird)

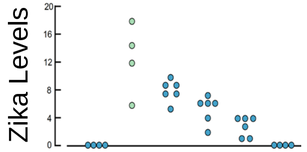


Deletion Platform to develop TIPs against *any* viral threat
(Autonomous & Gladstone)





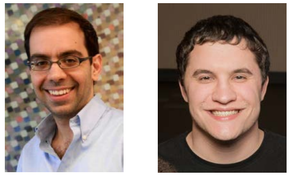
HIV TIPs (Del. Mutants)



Zika TIPs (Del. Mutants)

Existing Team

UChicago
Machine Learning, Outbreak Predction, Flu & Stochastic Modeling



Autonomous
TIPs, Viral Engineering, Multi-scale Modeling & Bioreactors

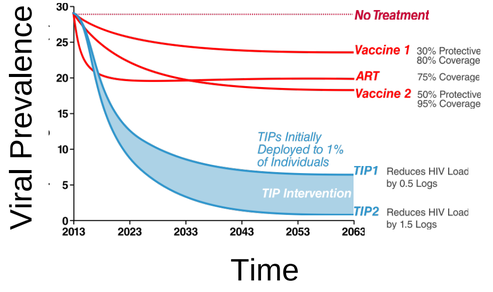
Gladstone/UCSF
TIPs, herpes & retroviruses, Multi-scale Modeling & BSL3 Bioreactors

CSU
Arboviruses, Mosquitos, Ticks, Sampling & Genomics

Ariel Weinberger: ariel@autonomous.bio

Population-Scale Impact

TIPs would *autonomously* transmit across reservoirs
(HIV Example)



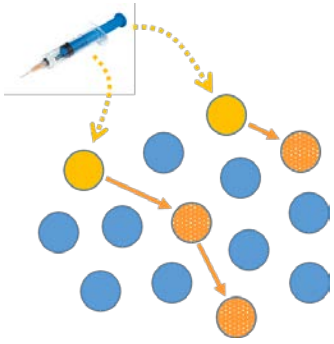
Our Targets

Tick-borne viruses
Mosquito-borne viruses
Simian retroviral threats
Influenza
Bat-borne viruses

Eradicating reservoir pathogens using transmissible vaccines

Scott L. Nuismer (University of Idaho)

Lassa fever
Zika
H7N9
MERS
Ebola
Hepatitis E



$$\sigma_{crit} = \left(1 - \frac{R_{0,V}}{R_{0,W}}\right)\left(1 - \frac{1}{R_{0,W}}\right)$$

$R_{0,V} > R_{0,W}$ → Autonomous eradication

$R_{0,V} < R_{0,W}$ → Reduced vaccination effort

Team and Expertise

Scott Nuismer
Host-pathogen coevolution
Mathematical modeling
Computational modeling

Jim Bull
Viral evolution
Mathematical modeling

Chris Remien
Mathematics

Key Results

Nuismer et al. 2016. Eradicating infectious disease using weakly transmissible vaccines. ***PRSB***
Bull et al. 2017. Transmissible viral vaccines. ***Trends in Microbiology***
Basinski et al. 2018. Evaluating the promise of recombinant transmissible vaccines. ***Vaccine***

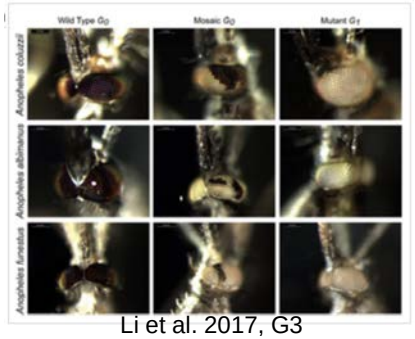
Our Objectives and Teaming Objectives

- **Guidelines for engineering effective TV's**
- **Engineer transmissible vaccine against target EID**
- **Proof of concept in laboratory populations**
- **Estimate key parameters in reservoir populations**
- **Forecasting tools for intervention outcome**

Contact: snuismer@uidaho.edu (208) 885 4096

Omar Akbari, University of California San Diego, Genetic Vector Control

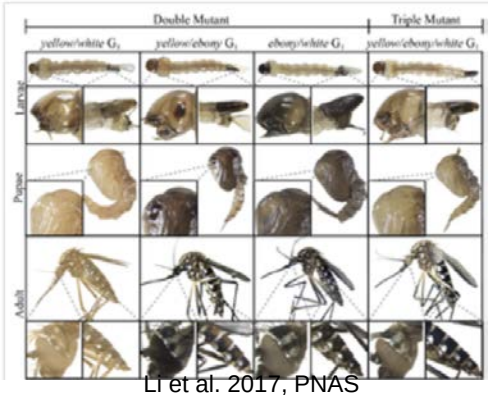
Project Overview



Li et al. 2017, G3

Buchman et al. Unpublished

- **Aim:** to develop new, scalable, genetic based approaches to prevent pathogen spillover and transmission from animals and vectors into humans.
- **Approach:** Target vectors (enzootic/epizootic, bridge, human) with genetic population replacement and/or genetic population suppression strategies to prevent zoonotic disease transmission to vertebrate hosts. This approach will also be evaluated in lab cage studies and integrated into scalable and easily deployable sexing and production strategies.
- **Challenges:** Developing genetic lines for target species
- **Phases:** Phase I: Develop and evaluate novel genetic zoonotic vector control technologies/ Phase II: Field trials



Li et al. 2017, PNAS

Teaming Overview and Objectives

- **Team needs:** epidemiologists and virologists that specialize in disease modelling and surveillance
- **Relevant experience:**

Technologies for genetic control strategies
1) Cas9 expressing *A. aegypti* lines (Li et al. 2017, PNAS)
2) Zika virus refractory *A. aegypti* lines (unpublished)
3) Dengue virus refractory (serotypes 1-4) *A. aegypti* lines (unpublished)
3) CRISPR/Cas9 tools for malaria vectors (Li et al. 2017, G3)
4) novel gene drive, genetic sexing and SIT approaches

- **Institutional assets:** TIGS, ACL-2 and BSL 2&3 facilities
- **Our goal:** Genetic vector control to prevent zoonotic disease transmission
- **Collaborators**: a focus in epidemiology, virology and disease modelling to inform the best vector target(s), release thresholds and timing for this approach

Impact

- **Anticipated impact:** Novel, scalable zoonotic vector control tools, which can be incorporated into zoonotic disease management programs
- **Potential applications:** Vector/zoonotic disease prevention programs and zoonotic disease research studies
- **Milestones:** 1. Identification and evaluation of anti-pathogen effectors and drives for pop. replacement; 2. Identification and evaluation of genetic tools and drives for pop. control strategies. The most promising approaches will undergo 3. Lab cage trials and 4. assessment for integration into scalable production technologies
- **Technology transition:** Regulatory evaluations and approval of field cage trials, field release trials and commercial distribution

Contact Information – oakbari@ucsd.edu– (858)-246-0640

PI:David Mooney PhD, Donald Ingber MD PhD, Wyss Institute

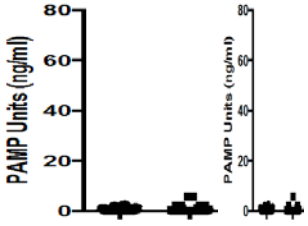
"Developing autogenous vaccines against zoonotic viruses in wild animal reservoirs to block species jump"

Project Overview: Develop autogenous vaccines to zoonotic viruses in animal population reservoirs

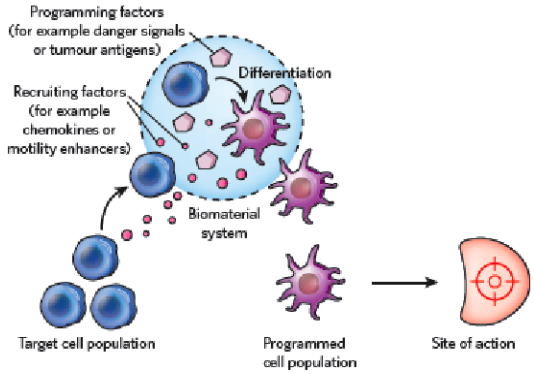
DARPA Sepsis DLT BAA 11-30, 12-36
(Ingber/Super)
"Generic pathogen capture technology from blood"
(Kang et al.,2014; Cartwright et al., 2016)

> 90 species, including CMV, Dengue, Ebola, EBV, Hep B, C, HIV, HSV 1,2, Influenza, A, Marburg, RSV, SARS-CoV, WNV

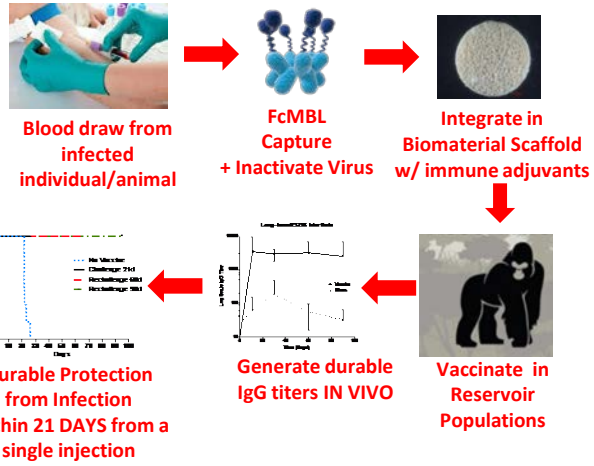
FcMBL Capture Protein



"Artificial Lymph Node" Programs
Dendritic Cells in situ
(Mooney/Doherty)
Effective Cancer Vaccine
(Ali et al Nat Material 2009)



PREEMPT Autogenous Vaccine
(Ingber/Super/Mooney/Doherty)



Teaming Overview and Objectives

Team:
- Wyss Faculty: George Church (genetics), Jim Collins (modeling)
- Wyss Technical Staff: Doherty (vaccines), Super (protein engineering).

Relevant experience:
- Mooney - particulate vaccines, Ali et al., 2009, 2015, Kim et al., 2015.
- Ingber - broad-spectrum pathogen capture, Kang et al., 2014, Cartwright et al., 2016.

Institutional assets:
- Collaborative agreements in place for all Boston Hospitals and Universities, BSL2 laboratories, (access to BSL 3&4) NIH Influenza funding, DARPA Chips, DLT and ThoR funding, DOD TVS funding

Technical challenges & collaborations:
- We can produce vaccines, collaboration on modeling

Impact

What is the anticipated impact of the team's success?
- Understanding spread of virus in animal populations. Spread of mutations, Surveillance technology. Vaccination in the bush.

List of potential applications enabled by this technology:
- Vaccines against Adenoviridae, Arenaviridae, Astroviridae, Bunyaviridae, Coronaviridae, Filoviridae, Flaviviridae, Hepadnaviridae, Herpesviridae, Orthomyxoviridae, Papillomaviridae, Polyomaviridae, Retroviridae, Togaviridae

Unique metrics and milestones the team aims to achieve:
- Develop vaccines against 1-2 zoonotic viruses in animal models

How will the team pursue transition of this technology?
- Through DARPA PM contacts to DOD

Michael Super. Michael.Super@wyss.harvard.edu. 617 432 7013

Michael A Jarvis, University of Plymouth

Aim

- Cytomegalovirus (CMV)-based disseminating vaccine to target inaccessible animal populations involved in transmission of highly virulent emerging viruses to interrupt transfer to humans.

Approach

- Ebola virus (EBOV) in NHPs as model for 'proof-of-concept' for other known and unknown highly pathogenic zoonotic viruses with pandemic potential in inaccessible animal populations.
- CMV-based EBOV vaccines are protective.

Objectives & Milestones

- Experimental validation of disseminating vaccines to control EBOV in NHPs (as model emerging virus in animal transmission species).
- Understanding of the dissemination characteristics of the CMV vaccine in the NHP target species.
- Initial safety and immunogenicity/ protection durability profile.

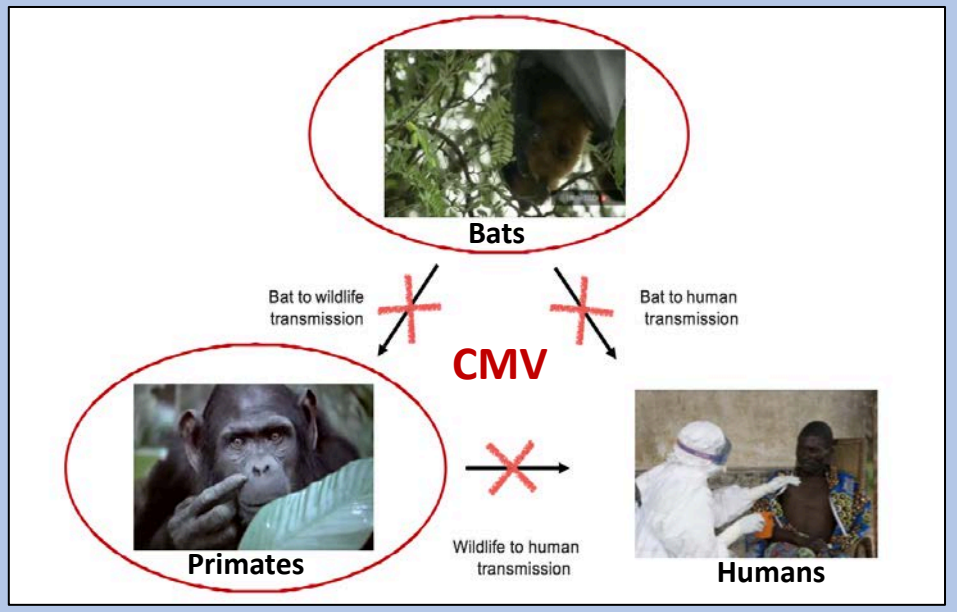
Key Challenges

- Maintenance of protective capacity while ensuring animal-to-animal spread of vaccine.
- For wildlife, CMV high host specificity increases environmental safety, but will require use of species-specific CMVs.

Impact

- Provides first proof-of-concept for innovative vaccine capacity, especially suited to harsh tropical regions.
- Technology can be applied towards targeting inaccessible animal reservoir and spill-over species for known and future zoonotic pathogens ('plug and play' antigen) – capacity currently unavailable using conventional vaccines.

Model



Team Overview & Infrastructure

- Michael A Jarvis – CMV vaccine development and immunology.
- Heinz Feldmann – Animal models of highly pathogenic viruses and vaccine development against these pathogens.
- Peter Barry – CMV transmission and primate models of CMV.
- Scott Nuismer – Mathematical modeling of transmissible vaccines.
- **Institutional Assets:** BAC-based mutagenesis capability, BSL-2 and BSL-4 level facilities for vaccine transmission and EBOV challenge studies, mathematical modeling programs.
- **Collaborators sought:** Companies with vaccine production and manufacture expertise.

Transitioning

- Establishment of key relationships with pharmaceutical companies possessing vaccine manufacture expertise.

www.thejarvislab.com

Dr. Simon Anthony: sja2127@cumc.columbia.edu

COLUMBIA UNIVERSITY | MAILMAN SCHOOL of PUBLIC HEALTH

Describe zoonotic pool

1. Viral discovery

Assess zoonotic 'potential'

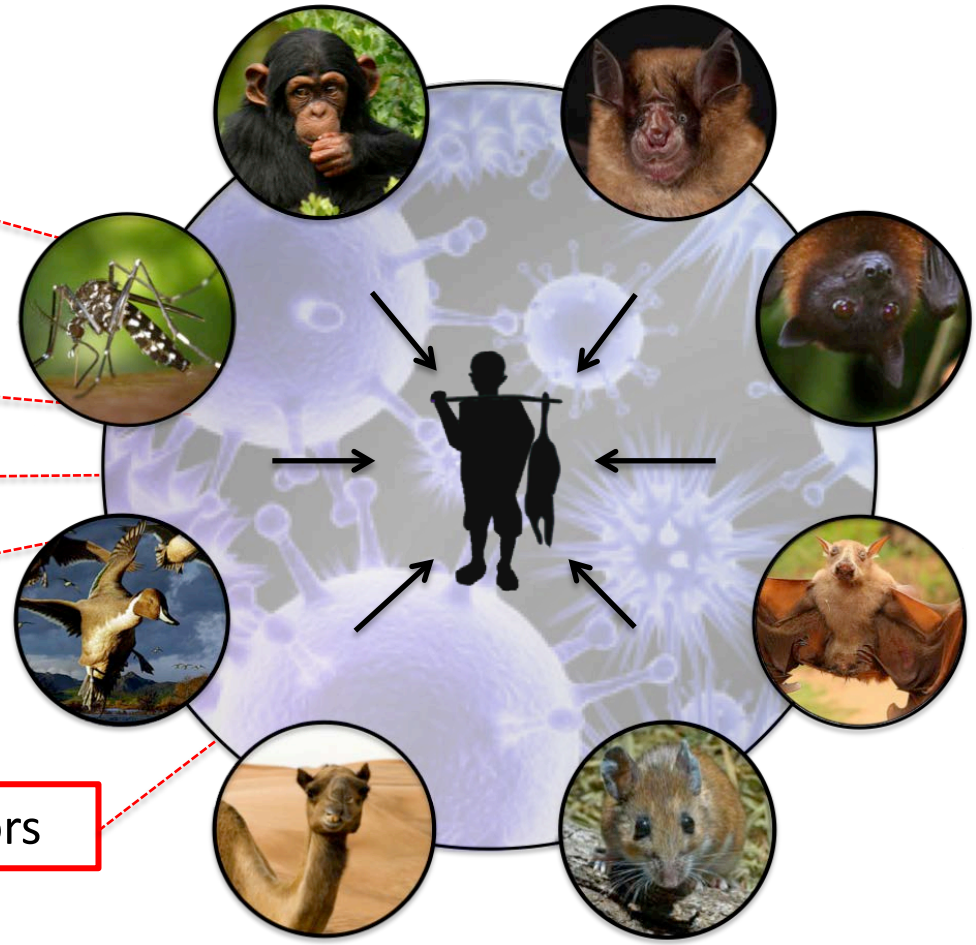
2. Enter human cells

3. Replicate to high levels

4. Antagonize interferon

Assess 'likelihood' of spillover

5. Ecological and behavioral factors



Froggi Jackson PhD, Gryphon Scientific

Project Overview

Scientific Expertise and Analytics for Human and Animal Health

SMEs with experience in epidemiological modeling, zoonotic and vector-borne disease biology
- Skills in public health-related risk assessment and analysis
- Applicable to both TA1 and TA2, including analyses of preemptive/intervention strategies

Access to relevant datasets and tools developed on previous projects
- Commercial animal farm and population numbers at the county level in US
- Model of agricultural systems supporting National Bio and Agrodefense Facility SSRA
- Tick-borne disease incidence and distribution in US regions
- Mosquito-borne disease incidence in Central and South America
- Disease outbreak risk assessment tool – risk of disease spread to US from abroad
- Emerging disease outbreak assessment tool - for international public health officials

GRYPHON SCIENTIFIC

Teaming Overview and Objectives

- Small research and consulting firm
  - Over 50% hold advanced scientific degrees (MS, PhD)
  - Fields ranging from microbiology to health physics
- Data and modeling decision support
- Preparedness and response planning
- Expertise in scientific communications

- Small Business
- GSA Schedules 84 and 00CORP
- Major clients: HHS, including NIH, CDC
  DHS
  DoD, including DTRA

Impact

Our expertise advances project outcomes and enhances the quality of deliverables
- Detailed technical understanding of disease emergence and spread, both nationally and internationally
- Inclusion of risk assessment and mitigation strategies into products
- Inclusion of policy and planning activities and recommendations
- Development of communications and training materials

Our access to existing datasets advances project timelines

Contact Froggi Jackson – froggi@gryphonscientific.com – 240-485-2542

Centers for Disease Control / Emory University / Uganda Wildlife Authority / Njala University

"Protecting the war fighter from Marburg virus and Sosuga virus by penetrating their natural reservoir bat population with countermeasures to purge the agents from nature"

Project Overview

Egyptian rousette bat

- **Goal** -Eliminate Marburg and Sosuga viruses from African cave-dwelling Egyptian rousette bats (ERB)
- **Approach** -Risk map the human/bat virus interface, utilize a live, naturally occurring transmissible bat virus modified to express antigenic Marburg virus and Sosuga virus epitopes for introduction into tens of thousands of juvenile bats throughout Africa to gain herd immunity
- **Challenges** -Define and quantify the interaction between humans and Egyptian rousette bats
  -Use surveillance, cell culture, NGS to study genetic bottlenecks needed for bat-to-human transmission
  -Identify a horizontally transmissible, minimally-pathogenic virus that is specific for Egyptian rousettes
  -Utilize reverse genetics to insert Marburg/Sosuga virus epitopes into recombinant virus countermeasure
  -Demonstrate immunogenicity, transmissibility and immunity to Marburg/Sosuga virus challenge
  -Use experimental infection/transmission studies in captive bats to parameterize coefficients necessary to calculate R_0 and model countermeasure spread and Marburg/Sosuga elimination
- **Structure** -TA1: Use micro-GPS technology and established African partners to locate, survey, sample African bat colonies to quantify spillover risk; Use Rousettus and human cell lines to find bottlenecks
  -TA2: Use established bat, virus, and genetic systems to validate and model countermeasure efficacy and impact

Teaming Overview and Objectives

- **CDC-Viral Special Pathogens Branch** (Jonathan Towner, Stuart Nichol)
- *Experience* – Virologists, ecologists, reverse geneticists (Virol 25531184, 24074586, 26122472) with decades of experience with BSL-4 viruses, identified ERB as Marburg & Sosuga virus reservoir (PLoS Path 19649327, 23055920; JWD 25919464), extensive experience and partners in Africa
- *Assets* – BSL-4 lab, Only Egyptian rousette bat breeding colony, proven Marburg virus bat transmission and immunity model (Nature Sci Reports 28821722, Nat Comm 28194016), current DoD funding-**HTDTRA 14-1-0016**.
- *Challenges addressed* – Identify, culture, reverse engineer bat virus and conduct all immunization, transmission and challenge studies
- **Emory University-Dept of Biology** (Rustom Antia)
- Experienced mathematician expert in modeling dynamics of pathogens, populations, immune responses (Proc Biol Sci 27798311, Nature 14668863).
- *Challenges addressed* – Use experimental data to quantify countermeasure transmission and efficacy of Marburg/Sosuga reduction.
- **Uganda Wildlife Authority, Uganda** (Patrick Atimnedi)
- **Njala University, Sierra Leone** (Aiah Lebbie)

Impact

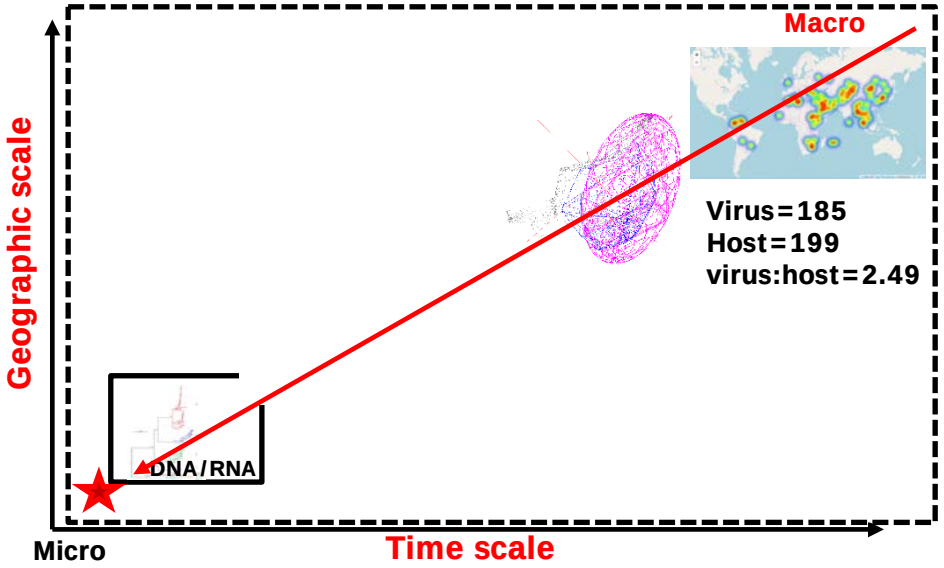
- 70% of all human pathogens are zoonotic, with many high consequence agents being bat-borne RNA viruses (e.g. Marburg, Ebola, Nipah, SARS, and Hendra virus)
- Simultaneous elimination from nature a Tier 1 Select Agent with Ebola-like pandemic potential and a newly emergent highly pathogenic paramyxovirus that might be only steps away from high transmissibility to humans
- Establishment of a generalizable strategy to eliminate other highly virulent bat-borne pathogens like Ebola
- Provide proof-of-principle for selectively removing a pathogen from a large mobile and wild metapopulation while not eliminating a species otherwise critical for ecological balance.

Contact Information: Dr. Jonathan Towner, jit8@cdc.gov, +1 404 639 4561

Gustavo Machado, North Carolina State University, Multiscale eco-epidemiology

Project Overview

- Characterize and quantify the probability of a viral disease emerge from rodent reservoirs: a multiscale model.
- **Micro:** Occupancy and network models of virus based on landscape, reservoir traits, and genetic signatures.
- **Macro:** Identify areas, species, livestock, villages at risk.
- **Phase I:** Identify environmental conditions where viruses occur in rodent reservoirs (mapping).
- **Phase II**: Determine rodent-virus contact and transmission rates using genetic networks (Phase 1).
- **Phase III:** Forecast the propensity of virus spillover to surrounding areas and species.
- **Phase IV:** Validate model predictions in the rodent species, communities and localities predicted.



Teaming Overview and Objectives

- **Years of collaboration and infectious disease modeling.**
- **Well equipped laboratory facilities.**
- Multidisciplinary (epidemiologist, computer science, disease ecology, remote-sensing, biogeography).
- Experiences in early disease detection for WHO during Zika emergency.
- L. Escobar (Virginia Tech), .A.T. Peterson (U. Kansas); H Qiao (Chinese Acad. Sciences).

Goals:

1. Data collection, curation, and analyses to identify the most candidate rodent species and location for spillover events worldwide.
2. Model validation via sites, species, season, habitat, forecasted-surveillance.

Impact

- Global spatio-temporal observatory for emerging and re-emerging viruses from rodents (order Rodentia).
- Generate a global early warning-system with targeted epidemiological surveillance (e.g. hospital, city, state, countries).
- Milestones:
  - Use in human an animal health alert systems.
  - The project will facilitate the identification of hotspots of emerging threats in a near real-time system.
- The codes and data will be made open-source and, we will provide analytical training to the country identified as hotspot for spillover.

Contact Information – gmachad@ncsu.edu– (919) 513-6249

Cary Institute of Ecosystem Studies

Barbara A. Han, Ph.D

Project Overview

- **Key Expertise: Predictive analytics using machine learning**. We draw from diverse data streams describing intrinsic organismal features to predict hosts, vectors, pathogens with greatest zoonotic potential.
    - Past predictions, subsequently confirmed: novel carriers of human zoonoses in rodents (US); new bat carriers of filoviruses (China); mosquito vectors of flaviviruses (global);
    - New, unpublished predictions: primates capable of sustaining sylvatic cycle of Zika virus in the Americas; zoonotic viruses with greatest potential for human-to-human transmission;
- **Contributions to PREEMPT objectives**: Our team generates data-driven predictions of organisms involved in the sylvatic transmission cycle (ie, **target species from which viral jumps are the most likely**); machine learning methods are applied to existing organismal data, and can be readily augmented and updated with new data (reported/collected)

Teaming Overview and Objectives

- **Team/Partners:** Han Lab (CIES), Drake Lab and members of UGA Center for Ecology of Infectious Diseases, IBM Watson Research Lab, members of AI / Data Science teams
- **Experience**: Members have pioneered: i) novel application of machine learning for organismal predictions, ii) novel machine learning approaches for bespoke ecological analyses; iii) novel data science methods to address technical challenges (missing data, sampling bias)
- **Team/Institutional assets**: history of collaboration; organismal data collation (mammals, mosquitoes, ticks); IBM Watson technology

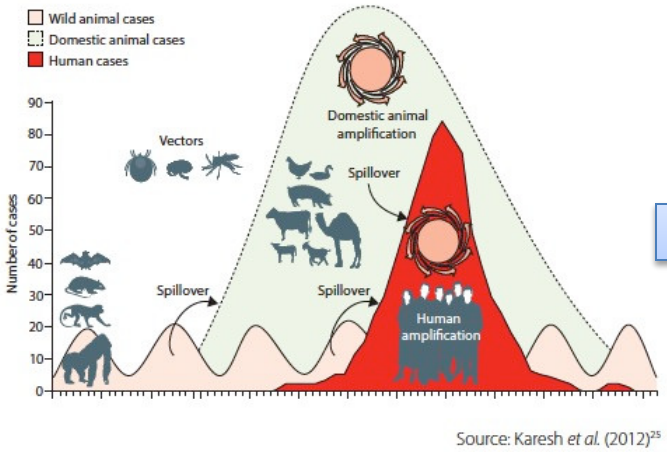
Impact

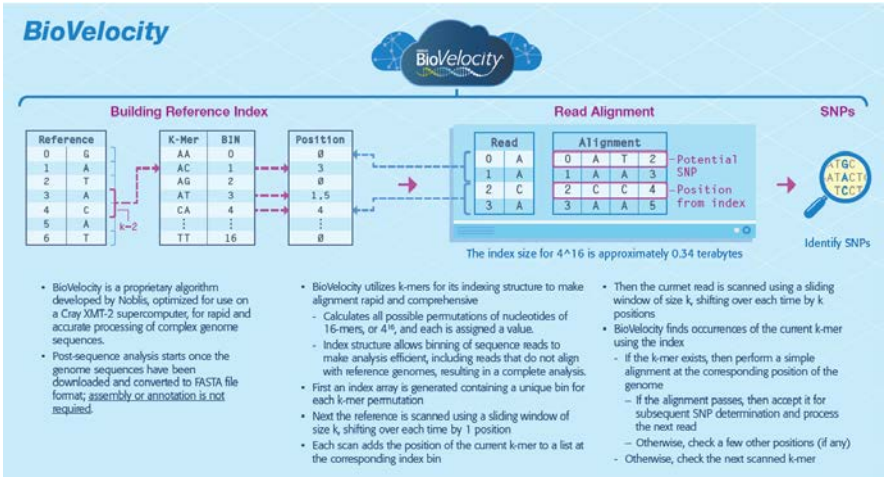
- Predictive modeling will leverage existing data to **target high risk organisms (hosts, vectors, viruses) comprising pre-spillover sylvatic cycles**. Algorithms can be updated to include new positive data, and are flexible to data type
- Analytical pipelines developed by our team can be folded into new biosurveillance / block-before-jump systems; models can be updated as new data become available
- Our team will assign **risk scores to rank order species/strains by likelihood of contributing to human spillover**

Contact Information – hanb@caryinstitute.org – 845-677-7600 ext 135 – www.hanlab.science

Sterling Thomas, PhD, Noblis Inc.

Predictive Bioinformatics





Teaming Overview and Objectives

- Noblis has a long history in bioinformatics focused in infectious disease research:
  - 2011 German E.coli outbreak
  - 2014 Ebola outbreak
- Created CRIPTIC informatics platform for evaluating and sharing data on emerging infectious diseases – Critical Reagents Program
- New MinION focused sequencing laboratory focused on in-field studies
  - Integrated with our single board compute research program (Raspberry Pi, Parallella)

Impact

- Noblis' BioVelocity platform supports the identification of genomic regions with high susceptibility to evolutionary pressure. Identifying these regions will allow the PREEMPT program to assign risk to Zoonotic reservoirs.
- Our approach will support the design of testing platforms for monitoring Zoonotic reservoirs.
- Success for our team is identifying genomic regions combined with evolutionary pressures and ranking those regions by risk. Our success metrics will be the number of regions and those risks.
- Noblis has a long history of successfully transitioning technology into production for warfighters and scientists.
  - We provide source-code and data to support implementation.

Contact Information: sterling.thomas@noblis.org – 571-422-7008

Metabiota, Inc.

Project Overview

- Leverage existing expertise and distributed surveillance infrastructure to implement ecological viral surveillance in regions at high risk for emergence events.
- Apply multi-scale, probabilistic suitability and transmission models to surveillance, host, environmental, and viral data to quantify the risk of viral emergence and identify contributing factors.

Teaming Overview and Objectives

- Team with deep infectious disease modeling and surveillance expertise.
  - 21 MD, DVM, and PhD scientists
  - >250 year of infectious disease experience
- Implementing partner for USAID PREDICT, conducting zoonotic field surveillance in 10 African and Asian countries identified as high risk for disease emergence.
- DTRA CBEP partner with operational experience focused on biosurveillance and biosafety/security in 14 countries across four Geographic Combatant Commands.
- Developed epidemic analytics for NGA, DIA, and In-Q-Tel.
- Specialized expertise in infectious disease suitability mapping, phylodynamic analysis, ecological surveillance, risk analysis, software development, data management, behavioral health interventions, and capacity building.
- Opportunities for collaboration in high throughput screening methods, evolutionary modeling, and preemptive intervention evaluation.
- Technical challenges include design and implementation of sampling methodology to support QS analysis and intervention evaluation.

Impact

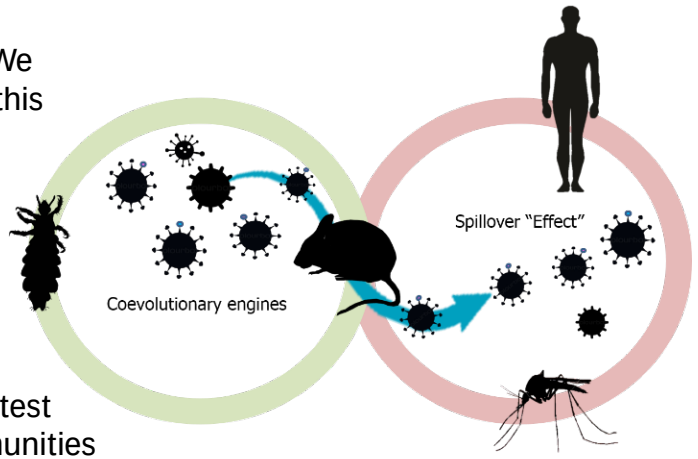
- Successful implementation of the project will result in development and calibration of stochastic models to evaluate the risk of viral emergence and transmission.
  - Viral, host, and behavioral drivers of emergence will be targeted *in silico* to identify interventions for evaluation.
- Analytic engines will be developed to production-quality and integrated into infectious disease analytic software, allowing for smooth, near-real-time surveillance data integration and sharing.
- Models, data, software, and interventions generated will have broad applications within a next-generation surveillance landscape targeting preemptive and early emergence events, resulting in reduced risk of high consequence outbreak events.

payscue@metabiota.com (607) 342 7977 bbrooks@metabiota.com

Sarah Zohdy, Auburn University, The Coevolution Effect

Project Overview

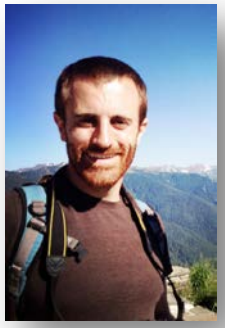
- Emerging zoonotic viral infections are associated with habitat degradation. We present a hypothesis to explain the eco-evolutionary **mechanisms** driving this phenomenon
- We developed an interdisciplinary model based in co-evolutionary linkages between obligate vectors and their hosts and introduce an experimental framework to evaluate this model



- **Phase I**: Formulate hypothesis, generate synthesis, field sampling
- **Phase II**: Test whether host-parasite systems are co-evolutionary engines
- **Phase III:** Integrate viral metagenomics to characterize viral diversity and test whether mosquito vectors can mobilize new viral variants into human communities

Teaming Overview and Objectives

Population genetics



Phylogenetic theory

Viral metagenomics

- We have dedicated field sites in the tropics, state-of-the-art viral discovery facilities (U. Wisc-Madison), genomics core
- Seeking collaborations with mathematical modelers

Impact

- Identify the ecological conditions that catalyze viral spillover events into human populations
- Present a scalable hypothesis that can be evaluated globally
- Measure viral diversity in wildlife, their obligate parasites and mobile vectors across landscapes to identify geographic regions of high viral diversity
- Generate a co-evolutionary model to be used by the broader epidemiological community to predict viral emergence hotspots

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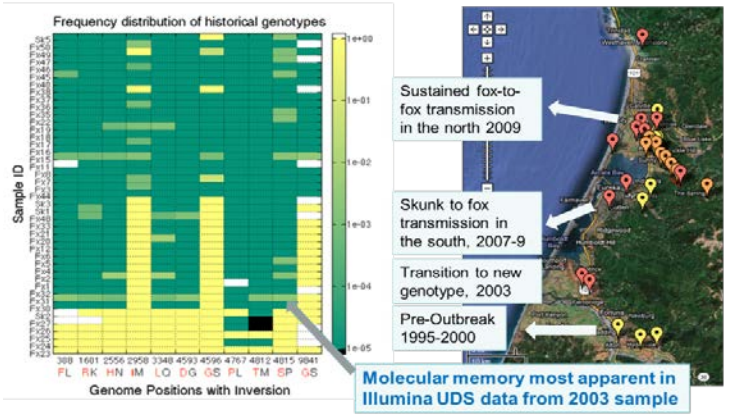
Predicting Cross-Species Transmission using Molecular Bioinformatic models

M. Borucki, LLNL

Concept Overview & Innovations

- CST is approached retroactively, empirically and using epidemiological/ecological tools.
- Objective: Create a multiscale, molecular model-driven approach to predict CST
  - Deep–sequencing to define circulating variant genotypes
  - Protein structure models with MD simulations to identify mutations likely to impact CST.
  - Validate predictions using reverse genetics.
  - Model will estimate the number and type of mutations needed to expand virus' host range.
- Technical challenges include development of predictive high-throughput screening assays and availability of crystal structures or high accuracy homology models of receptor-ligand interactions.

Molecular analysis restrospectively predicted CST of rabies virus



Teaming Overview and Objectives

- **LLNL Team:** Computational modelers Jonathan Allen and Adam Zemla, Virologist Monica Borucki
- **Relevant experience**: Use of computational modeling and virology to detect rare variants associated with CST; Experience with analysis of large data sets
- **Institutional assets:** High performance computing to allow extensive macromolecular docking and MD simulations; BSL-3 facility
- **LLNL has capabilities to address:** Analysis of deep sequencing data using error modeling, protein structure modeling and molecular dynamics models, molecular virology, animal models.
- **Need collaborators:** Biosurveillence partners for naturally infected samples, HT bioassay development

Impact

- **Impact:** A multiscale, molecular-based model for prospective analysis of viral populations from zoonotic samples for genotypes with characteristics that enable CST. These capabilities will allow probabilities of CST to be determined for circulating genotypes and guide design of intervention strategies.
- **Applications:** Biosurveillance and countermeasure capabilities will be expanded to address genetic variants that circulate at the subconsensus level. Protein structural models will prioritize variants according to predicted impact of viral phenotype. The result will be more accurate and rapid countermeasure.
- **Technology transition:** Collaborate with DoD and other biosurveillence labs for assembly of analysis pipeline in regions of probable viral emergence and integration of molecular information into countermeasure design.

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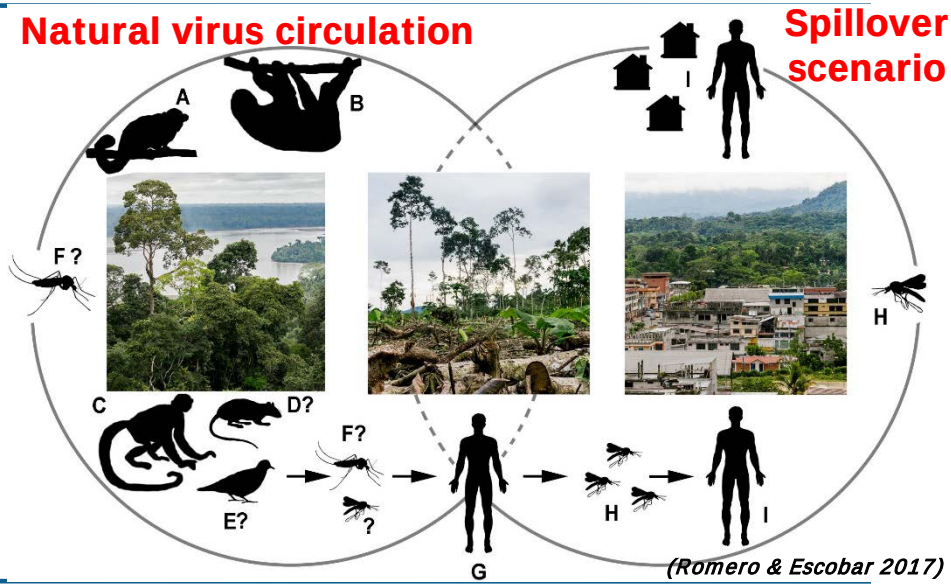
Luis Escobar, Virginia Tech, Team: “WhyWhere”

Project Overview

- ~320,000 unknown viruses that infect mammals (>3.6M all vertebrates). *(Racaniello 2017)*
- A good viral survey for a single species = $1.2 M. *(ibid)*
- *R***o** flu = 2-3, *R***o** malaria = 1-3000. *(Mills et al. 2004, Smith et al. 2007)*
- **Vector-borne** diseases kill 0.7 M people/yr worldwide, single most important disease problem of the military worldwide. *(WHO 2017, Leggat 2010)*
- Goal: Understand **Why** and **Where** “spillover” occurs = emphasis on vector-borne viruses. *(Romero & Escobar 2017)*



Teaming Overview and Objectives

- **Aims:**
  1. ***Reconstruct*** *habitat conditions before-during* ***spillover*** *events of arboviral diseases (e.g., outbreaks) using* ***satellite-derived*** *data.*
  2. ***Spatio-temporal forecast*** *of areas and seasons suitable for spillover events (dynamic atlas of risk).*
- **A.T. Peterson** (U. Kansas); **H Qiao** (Chinese Acad. Sciences); **G Machado** (North Carolina State U.).
- **~300 publications** in disease forecast; vast experience in vector-borne diseases; multidisciplinary, computer facilities on-campus.
- **Top 6 solvers of DARPA** Chikungunya challenge.
- **We invite** epidemiologists of arboviral diseases in Africa and the Middle East.

Impact

- Develop and implement a global workflow for applied **digital epidemiology**.
- Collective (multi taxa/multi-site), instead of individual (single outbreak), assessment of the **landscape** conditions facilitating spillover.
- Identify landscape conditions in **hotspots** of spillover to **predict** areas of future spillover => guide surveillance.
- Quantify **temporal lag** between landscape change outbreak => early warning systems.
- **Release data** & **code** generated to explore other non-arboviral spillover events.

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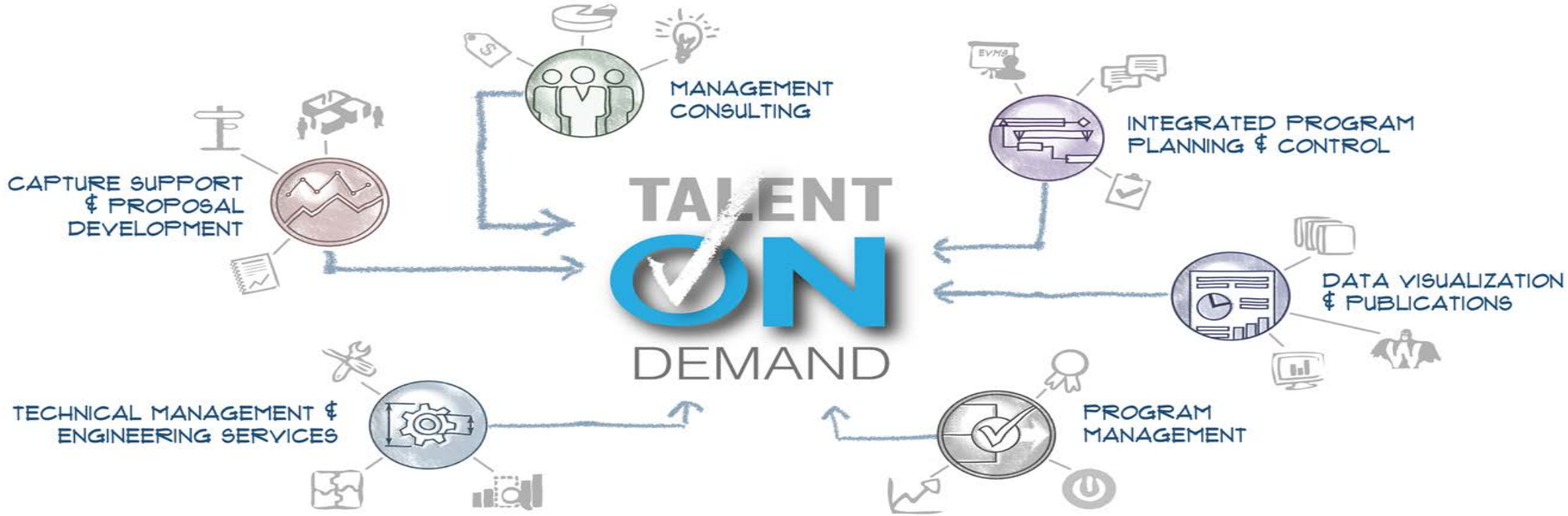

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Slides Requested to be Shared with Community

Peter Daszak, EcoHealth Alliance, “Defuse EIDs”

Project Overview

- Using our state-of-the-art hotspot and viral-host richness predictive machine-learning models, we will target the most important hotspots for viral surveillance in key wildlife zoonotic reservoirs
- We will sequence viral spike proteins and host cell receptors to analyze co-evolutionary patterns and develop predictive models of which viral strains are most likely to jump host and emerge
- We will work with our unique cell lines, and humanized lab animal models to manipulate known viruses with spike proteins of novel viral strains to test our spillover models and identify key targets for intervention
- To identify the best pathway to reduce the risk of viral emergence, we will use mathematical models of inter-species viral transmission that are ecologically and evolutionarily explicit, and test the feasibility of different approaches (gene drives, wildlife vaccination, wildlife population manipulation, behavioral modification strategies).
- Using captive bats and rodents, and close relatives of viral targets, we will test our model predictions in the lab
- We will scale these approaches up to wildlife populations at closely monitored caves and mesocosms
- We will demonstrate spillover blocking proof-of-concept for a select high profile target (e.g. a bat CoV) in the wild

Teaming Overview and Objectives

- Partners: EcoHealth Alliance; University of North Carolina Baric Lab; Columbia University Lipkin Lab; NIH Rocky Mountain Lab; Wuhan Institute of Virology China; and Duke NUS (Singapore)
- Experience: World leaders in modeling disease emergence (Hotspots, host-viral traits, missing zoonoses, identifying number of unknown viruses/GVP – *Nature*, *Science*). Hundreds of thousands of samples from high profile wildlife collected during last two decades globally. Intensive work on key emerging viruses (Nipah, SARS-like CoVs, SADS, MERS, EBOV).
- Institutional assets: Collaborative agreements in place for Infectious disease research in humans and animals in 15 countries, including China, Malaysia, Indonesia, Jordan, Liberia and Cote d’Ivoire; BSL 3 and 4 laboratories with rodent and NHP research and genetic engineering capabilities; Current DTRA, USAID, NIH contracts for emerging viral research.
- Technical challenges for partnerships: strategies to block spillover, incl. gene drives.

Impact

- New tech, capability: new predictive models of spillover; targeted sequence/isolate collection; viral spike sequence database.
- Potential applications: new gene drive approaches, wildlife vaccines; new wildlife population behavior/manipulation technologies.
- Metrics: Phase 1: rapid collection of novel viral sequences. Phase 2: spike protein generation, binding assays, chimera production. Phase 3: successful lab and mesocosm experiments. Phase 4: proof-of-concept blocking spillover.
- Tech transition: All products will be open source and public domain; tech will be field-tested in mesocosms and shared with our multiple international partners.

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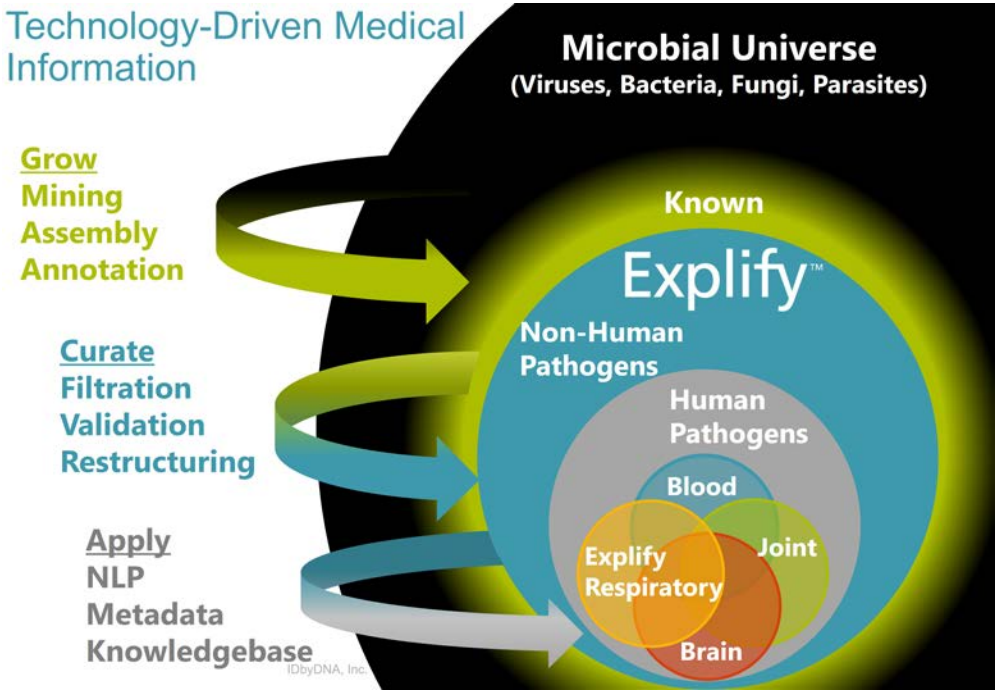
IDbyDNA: Identify any microbe, from any sample, anywhere in the world

ULTRA-FAST, COMPREHENSIVE AND INTERACTIVE METAGENOMICS ANALYTICS PLATFORM

- Proprietary DNA/RNA search engine for NGS-based discovery and diagnosis
- Accurately identifies known and novel microbes, hypothesis-free
- Cloud-based, deployable anywhere in the world
- Generates results in minutes



Example Applications:

- Identified ZIKA virus genotype in first documented death[1]
- Explify™ Used in commercially available CLIA/CAP validated clinical Dx
- >500 Academic, government, and commercial institutions are using Taxonomer.com
- Detects pathogens not included in the database for public health emergencies
- QC Detects viral contamination in biological manufacturing processes

1. Swaminathan, Schlaberg, et al. September 28, 2016, NEJM

Contact: Jeff Field, CCO, jfield@idbydna.com

Guidance for Proposers Day Slide

- Follow the general guidance to include the information requested.
- DARPA strongly encourages establishing teams to address all technical objectives/phases to ensure the expertise and capabilities necessary to meet program goals.
- Provide a concise and informative summary of your proposal interest.
- Unclassified information only.
- Only one slide will be presented.
- Please submit in MS PowerPoint (preferred) or equivalent file format.